ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cancer Drugs Fund rapid review of NICE Guidance TA309

Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

Confidential until published

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1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is in the process of assuming responsibility for the Cancer Drugs Fund (CDF). The CDF provided a mechanism for some cancer treatments, which failed to receive a positive recommendation when originally appraised for clinical and cost effectiveness for general use in the NHS, to be provided on a case by case basis to selected patients referred to the CDF by their clinician. As part of the transition, a number of historic technology appraisal decisions are being rapidly reviewed to determine the future status of treatments currently provided only through the CDF, i.e. whether they may now be recommended for general use, continue within the scope of the revised CDF scheme, or not be provided at all through the NHS. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool has been commissioned to review the company submission to assist a NICE Appraisal Committee (AC) in reconsideration of NICE Guidance TA309. The original Single Technology Appraisal (STA) was conducted in 2013-14 and final NICE guidance was issued in April, 2014 and did not recommend pemetrexed maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) following previous treatment with pemetrexed and cisplatin for use in the NHS.[1]

2 CONTEXT AND APPROACH TO RAPID REVIEWS

To allow these rapid reviews to proceed with the minimum risk of delay, the expected procedures have been restricted in scope for the company making a resubmission and for the Evidence Review Group (ERG) who is tasked with providing an independent assessment of the company submission. It is assumed that the primary clinical effectiveness data will remain essentially unchanged from the original appraisal and therefore no additional clinical evidence will be accepted by NICE. The cost-effectiveness analyses included in the company evidence submission needs to reflect the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) ICER(s) as identified in the published guidance. It is anticipated that the main areas to be considered by the AC will relate to changes in the costs associated with treatment including any special NHS pricing agreements agreed since the original appraisal was carried out.

3 SPECIFIC DIFFICULTIES WITH THIS RAPID REVIEW

An unusual feature of the original appraisal concerns the late clinical evidence presented to the AC by the ERG at the meeting during which the content of the Final Appraisal Determination (FAD) was decided (25th September, 2013). The ERG highlighted a controversy related to the estimation of overall survival (OS) gain attributable to pemetrexed

maintenance therapy and was particularly concerned about how survival beyond the clinical trial data should be estimated. The ERG presented results of a new analysis of the PARAMOUNT trial data,[2] which demonstrated that parametric survival modelling in this instance was unnecessary to obtain a reliable value for survival gain, since the long-term life expectancy of patients beyond disease progression was independent of prior treatment and could be disregarded (other than for minor adjustment to differential timing). On this basis it was estimated that pemetrexed maintenance therapy was associated with about 3.5 months of additional life years per patient (ERG 2nd Addendum 27 September, 2013). Due to the lack of time available prior to the AC meeting it was not possible for the ERG to fully develop this scenario for use within the structure of the decision model and it was only possible to indicate a rough estimate of the expected ICER of approximately £74,500 per QALY gained, which the AC considered sufficiently robust to form a basis for their decision. This presents a particular difficulty in relation to the current rapid reconsideration of TA309, since a clearly defined baseline scenario with a precise ICER was never previously established directly from the decision model.

4 METHODS

4.1 Establishing a baseline scenario

The company has submitted a version of their original decision model, which has been modified in an attempt to reflect the various amendments, corrections and options considered appropriate by the AC at the time of the original appraisal. This model has been carefully reviewed by the ERG and the ERG notes that some of the recommended changes have not been fully or correctly implemented by the company. These relate to:

- The assumption that fewer pemetrexed continuation patients receive post-progression chemotherapy, than best supportive care (BSC) patients (referred to as Mod_3)

- Use of ERG generic docetaxel treatment cost estimates (referred to as Mod_6)

- ERG survival models (referred to as Mod_13).

The ERG has introduced these changes to the recently submitted model to ensure consistency with the model logic that was previously used by the ERG and accepted by the AC, following the model formula amendments previously reported (see Appendix B for details of these changes, and Appendix C for the ERG assessment of the company's implementation of specified changes in their revised base case model). Mod_3 increases the

estimated ICER by £1,924 per QALY gained, and Mod_6 increases the ICER by £182 per QALY gained.

The main difficulty in achieving an estimated ICER similar to that used in the preparation of the final decision (£74,500 per QALY gained) within the limitations of the resubmitted decision model is that it is necessary to apply appropriate lifetime survival extrapolations beyond the trial data to allow long-term treatment and care costs to be estimated. In reality it will never be possible to reconcile accurately results of a model structured around the assumption of parametric survival models, and the more accurate estimate of survival gain which requires only the evidence from the clinical trial data that there is no difference in post-progression survival attributable to continuation of pemetrexed monotherapy. The ERG had demonstrated that the same long-term projective function should be used for both treatment arms, but there are a wide variety of ways in which this can be introduced into the model depending on the time at which extrapolation is introduced into each arm, and any rules adopted to govern how this is implemented.

The ERG had developed two different approaches to this procedure which gave quite different results and neither precisely matched the most reliable estimated survival gain attributable to continuation therapy (+3.49 months). These were implemented in the company model through a logic modification (referred to as Mod_13). When Mod_13 is set to value 1 (option 1) the ERG OS exponential model is applied as detailed in the original ERG report. When Mod_13 is set to value 2, the time when the ERG OS model is introduced is governed by the time in each arm at which the same proportion of trial patients remain alive (in this case 37%).

In order to achieve a reasonably representative base case scenario against which to test the marginal effect of any additional relevant changes to non-clinical model parameters, the ERG selected the survival projection option giving the estimated survival gain closest to the expected value. Using Option 1 results in an estimated OS gain of 3.376 months under-estimating gain by 0.114 months, whereas Option 2 results in a lower OS gain of 3.071 months (under-estimating by 0.419). Therefore Option 1 provides a closer match to the non-parametric estimate. The remaining underestimate was then corrected by applying a correction factor to the model ICER proportional to the ratio of the target ICER to the uncorrected model ICER (x 1.037). The resulting base case ICER is then £74,371 per QALY gained, which is sufficiently close to the ‘approximately £74,500’ quoted in the AC documentation to allow the likely impact of changes to the NHS price of pemetrexed, and to other relevant costs, to be assessed with some confidence.

The application of the adjustment factor is through a simple post-hoc multiplier applied to the model estimate of incremental quality adjusted life years (QALYs), without altering the model logic in any way. Given the finding that there is no difference in post-progression survival between treatments in the PARAMOUNT trial, all the incremental survival benefit occurred prior to disease progression, so the health-state utility value applied to both trial arms is identical and has no differential influence on the size of the estimated ICER.

4.2 Relevant changes

Three changes affecting model cost parameters need to be considered when updating the original model results:

- The Commercial Access Agreement (CAA) proposed by the company which reduces the net cost of pemetrexed treatment acquisition to the NHS.

- Changes in the cost of other drugs received by NSCLC patients following disease progression identified by the ERG. These are of two types: a second-line treatment (docetaxel) which was off patent at the time of the original STA and for which much cheaper generic versions are available and generally used in the NHS, and a Patient Access Scheme for another second-line treatment (erlotinib) has been amended subsequent to the original STA to further reduce its price to the NHS.

- The ERG has identified model parameters for which inflation has significantly increased the cost to the NHS of administering drug treatments, responding to treatment-related adverse events and providing on-going patient care.

The details of the ERG's changes to cost parameters, including sources of information, are presented in Appendix A. The sensitivity of the estimated ICER relative to the baseline scenario for each of these types of change is reported separately and in combination.

5 RESULTS

Table 1 summarises the results of taking **all** of these factors into account in the model. The additional cost changes result in relatively small increases in the size of the estimated ICER to no more than £77,000 per QALY gained. By contrast, the inclusion of the CAA price for pemetrexed reduces the estimated ICER substantially to fall within the range of £[redacted] to £[redacted] per QALY gained.

Table 1 Sensitivity of estimated deterministic ICER to cost variations **and** proposed company CAA price of pemetrexed

Scenario	Original pemetrexed price	CAA pemetrexed price
Pragmatic baseline scenario	£74,371	£[redacted]
Baseline + changes in drug costs	£74,405	£[redacted]
Baseline + NHS cost inflation	£76,688	£[redacted]
Baseline + changes in drug costs + NHS cost inflation	£76,701	£[redacted]

ICER=incremental cost effectiveness ratio; CAA=Commercial Access Agreement

6 CONCLUSION

The approach taken by the ERG to recalibrate the company model to reflect the decision scenario previously employed by the AC as the basis for the published guidance is not ideal. However, the ERG considers that it appears to be generally robust to the inclusion of the full range of previous model amendments, and also to the cost and price parameter changes that have occurred since the company model was originally developed.

It appears that NHS cost inflation is more influential on cost effectiveness than the changes in NHS drug acquisition prices. However, neither is sufficient alone or in combination to increase the estimated ICER by more than £2,500 per QALY gained. The estimated ICERs, when the proposed CAA price for pemetrexed is applied, fall within the narrow range of £[redacted] to £[redacted] per QALY gained, whilst the best available estimate for mean survival gain exceeds 3 months (+3.49 months).

APPENDIX A: Details of ERG alterations to model cost parameters

Item	Detail	Old value	New value	Source
Chemotherapy delivery	HRG SB11Z day case oral	£192.32	£171.25	NHS Reference Costs 2014/15[3]
Chemotherapy delivery	HRG SB12Z day case simple parenteral	£207.88	£257.11	NHS Reference Costs 2014/15[3]
Chemotherapy delivery	At home by community nurse (hourly rate)	£64.00	£67.00	Inflated by HCHS inflation index (PSSRU 2015)
CT scan	Outpatient 2 areas with contrast	£132.99	£121.68	NHS Reference Costs 2014/15[3]
CT scan	Outpatient 3 areas with contrast	£150.88	£124.10	NHS Reference Costs 2014/15[3]
Clinical oncology consultation	Specialty 370 consultant-led	£119.99	£167.12	NHS Reference Costs 2014/15[3]
Clinical oncology consultation	Specialty 370 not consultant-led	£91.00	£103.37	NHS Reference Costs 2014/15[3]
Hospitalisation costs	Various	Various	Uplifted by 5.93%	Inflated by HCHS inflation index (PSSRU 2015)[4]
Radiotherapy preparation	HRG SC47Z Preparation for simple RT with imaging & simple calculation	£240.00	£288.13	NHS Reference Costs 2014/15[3]
Radiotherapy delivery	HRG SC22Z Deliver a fraction of treatment on a megavoltage machine	£91.00	£113.51	NHS Reference Costs 2014/15[3]
Docetaxel acquisition cost	80mg vial – replace with generic product 20mg vial – replace with generic product	£534.75 £162.75	£25.73 £7.47	eMIT 2015[5]
Erlotinib acquisition cost	Confidential PAS prices	Original	Modified	Details are confidential
Terminal care costs	Various	Various	Uplifted by 5.93%	Inflated by HCHS inflation index (PSSRU 2015)[4]

CT=computed tomography; PSSRU=Personal and Social Services Research Unit; eMIT=electronic market information tool; HCHS=Hospital and Community Health Service: PAS=Patient Access Scheme; RT=radiotherapy

APPENDIX B: MODEL AMENDMENTS

Details of amendments made by the ERG to the manufacturer's decision model submitted to the NICE Single Technology Appraisal of pemetrexed as maintenance therapy for NSCLC in April 2013

1) *Recalculation of mean pemetrexed acquisition cost per cycle*
This amendment is activated by a binary switch variable (Mod_1) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Resource!N47' with the following:

=IF(Mod_1=0,SUM(N45:N46),1481.37)

The mean cost per dose was obtained as follows:
For Males create a table of 100mg dose units equivalent to steps of 0.2m^2 BSA. Use a cumulative normal distribution function to calculate the proportion of patients who can be treated up to the maximum dose available in that step. Determine the number of 100mg and 500mg vials required to deliver the dose for that step. Use a SUMPRODUCT function to calculate the mean number of 100mg and 500mg vials required by Males, and multiple these by the vial unit costs to obtain the overall mean cost for Males. Note that a dose cap of 1000mg is applied on clinical advice. The same procedure is used for Females and then a weighted average cost for all patients is calculated using the balance between Males and Females in the population.
The BSA distribution parameters are derived from the Sacco survey data excluding adjuvant and neoadjuvant patients, as follows:

Males - mean 1.88568, standard deviation 0.17933

Females - mean 1.65503, standard deviation 0.17249

Males: Females ratio based on PARAMOUNT trial (313:226)

2) *Removal of inappropriate continuity correction applied to pemetrexed acquisition cost*s
This amendment is activated by a binary switch variable (Mod_2) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Pem!DM11' with the following:

```
=IF(Mod_2=0,AVERAGE(CW10,CW11),$D$4*BH10*PemCost
+$D$4*AVERAGE(BH10,BH11)*(propCTscans*pCTscans*cCTscan
+propconsults*pConsults*cConsult))
+IF(JMENcosts=1,AVERAGE(CX11,CX10)+AVERAGE(DD10,DD11))
```

Copy this formula into cells 'Pem!DM12:DM366'

3) *Removal of differential use of second-line systemic therapies following disease progression*
The amendment is activated by a binary switch variable (Mod_3) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Resource!N305' with the following:

=IF(Mod_3=0,IF(PSA=1,M305,F305),pBSCSyst)

Replace the formula in cell 'Resource!N306' with the following:

=IF(Mod_3=0,IF(PSA=1,M306,F306),pBSCSyst)

Replace the formula in cell 'Resource!F307' with the following:

=IF(Mod_3=0,F305/F304,1)

4) *Recalculation of mean docetaxel acquisition cost per cycle*
This amendment is activated by a 3-way switch variable (Mod_6) taking value 0 to use the original model logic, value 1 to apply the amendment using BNF prices and value 2 using eMIT prices.
Replace the formula in cell 'Resource!M376' with the following:
=CHOOSE(Mod_6+1,SUM(M373:M375),M375+800.06,M375+87.39)
The method of calculation is similar to that used for pemetrexed (see (1) above), with the following alterations:
- dosing steps are at 20mg intervals
- three vial sizes are used - 20mg, 80mg and 140mg
- the lowest generic BNF list prices are used (£154.61, £508.01 and £720.10 respectively)
- the best eMIT average contract prices are used (£11.13, £47.24 and £86.10 respectively)

5) *Use of the covariate adjusted EQ-5D model to determine utility values*
This amendment is applied by setting range 'QoLdata' to value 2.

6) *Use of the covariate adjusted PFS model*
This amendment is applied by setting range 'PFSdata' to value 2.

7) *Use of the covariate adjusted OS model*
This amendment is applied by setting range 'OSdata' to value 2.

8) *Inclusion of re-estimated costs of vitamin supplementation required for patients receiving pemetrexed*
This amendment is activated by a binary switch variable (Mod_10) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Resource!V57' with the following:
=IF(Mod_10=0,SUM(V55:V56),1.778275)
This amendment is based on assigning protocol supplementation doses to each cycle, and applying this to the number of PARAMOUNT pemetrexed patients per cycle as shown in CSR addendum Table S124.4.8.

9) *Re-estimation of PFS follow-up costs*
This amendment proved difficult to implement within the main logic of the model. Therefore, the necessary alterations were implemented directly into cells in the Results spreadsheet. This involved calculating an estimated revised follow-up cost for both BSCand pemetrexed, and also the net discounted cost of PFS follow-up care in each arm.
The amendment is activated by a binary switch variable (Mod_11) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Results!F50 with the following:
=IF(Mod_11=0,bscTFC,bscTFC-1550.64611+238.33899)
Replace the formula in cell 'Results!M50 with the following:
=IF(Mod_11=0,pemTFC,pemTFC-1606.71508+407.59520)
The calculation of follow-up costs is based on out-patient assessment every 4 cycles for pemetrexed patients, and at 3, 6, 12 and 18 months for BSC patients. The same number of CT scans are assumed in each arm, spread out pro-rata to the number of

patients attending each assessment. Patient numbers used are taken from the PFS Kaplan-Meier estimates. The cost per OP appointment is £119.99, and the cost perCT scan is £142.92, and are discounted.

10) *Re-estimation of terminal care costs*
This amendment is activated by a binary switch variable (Mod_12) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'JMEN_Resource!H45 with the following:

=IF(Mod_12=0,(E45/UKCPI_08)*UKCPI_11,3906.31)

This estimate is taken directly from an HTA report recently completed by the ERG for first-line chemotherapy for NSCLC, and encompasses costs of care for patients dying in hospital, in a hospice and at home, with all supportive community and voluntary services.

11) *Selecting alternate starting points for projection of OS*
This amendment is applied by setting ranges 'KMstopOSBSC' and 'KMstopPem' to the appropriate values:

For 15% survival use 41 & 47

For 20% survival use 36 & 44

For 25% survival use 41 & 47

12) *Substitution of ERG long-term model for OS projection*
This amendment is activated by a binary switch variable (Mod_13) with value 1 to apply the amendment and value 0 to use the original model logic.
The modification to the BSC worksheet requires the following changes:
- Set Cell AZ7 to " =0.00176541033416705 * 21 (This is the exponential risk parameter for a 21-day cycle)

- Set Cell AZ10 to "= AN10", then copy this formula to the range AZ11:AZ28

- Set Cell AZ29 to " =AZ28*EXP(-$AZ$7)" and copy this formula to range AZ30:AZ366

Replace the formula in cell AW11 as follows:
=IF(Mod_13=0, IF(Cycles<=IF($D$4=0,KMstopOSBSC,KMstopOSPem), 1-AN11/AN10, IF(OSModel=1, AQ11, IF(OSModel=2,AR11 ,IF(OSModel=3,AS11 ,IF(OSModel=4,AT11, IF(OSModel=5,AU11,AV11))))), 1-AX11/AX10)
Replace the formula in cell AX11 as follows:

=IF(Mod_13=0,(1-AW11)*AX10,AZ11)

Copy the range AW11:AX11, and paste the formula to the range AW12:AX366

The modification to the Pem worksheet requires similar changes:
- Set Cell AZ7 to "=0.00170103676595399 * 21

- Set Cell AZ10 to "= AN10", then copy this formula to the range AZ11:AZ17

- Set Cell AZ18 to " =AZ17*EXP(-$AZ$7)" and copy this formula to range AZ19:AZ366

All other changes are identical to those in the BSC worksheet.

APPENDIX C: ASSESSMENT OF IMPLEMENTATION OF SPECIFIED ERG MODEL AMENDMENTS IN THE LATEST COMPANY REVISED BASE CASE MODEL

ERG mod#	ERG specified change	Company implemented change	Assessment
Mod_1 Pem cost per patient	Resource!N47 = IF(Mod_1=0,SUM(N45:N46),1481.37)	New cost applied directly to Resource!E32 combined with CAA discount in Resource!F31	Correctly applied.
Mod_2 Mid-cycle correction error in Pem cost	Pem!DM11..(DM366) =IF(Mod_2=0,AVERAGE(CW10,CW11), $D$4*BH10*PemCost +$D$4*AVERAGE(BH10,BH11) *(propCTscans*pCTscans*cCTscan +propconsults*pConsults*cConsult)) +IF(JMENcosts=1, AVERAGE(CX11,CX10) +AVERAGE(DD10,DD11))	Pem!DM11..(DM366)=CW10 +IF(JMENcosts=1, AVERAGE(CX11,CX10) +AVERAGE(DD10,DD11))	Correctly applied for PARAMOUNT resource data option.
Mod_3 Remove differential in 2nd line systemic Tx use	Resource!N305 =IF(Mod_3=0,IF(PSA=1,M305,F305), pBSCSyst) Resource!N306 =IF(Mod_3=0, IF(PSA=1,M306,F306),pBSCSyst) Resource!F307 =IF(Mod_3=0, F305/F304,1)	Resource!F305 unchanged Resource!F306 unchanged Resource!F307 = 1	**Incorrectly applied. Amends costs of 2nd line treatment but does not change the cost of follow-up or the associated utility.**
Mod_4 Add missing blood product cost	Resource!F293 =IF(Mod_4=0,58,58+125)	Resource!H293 =F293+125	This is correctly applied (only relevant for PARAMOUNT resource data option)

Mod_6 Include generic cost of docetaxel	Resource!M376 =CHOOSE(Mod_6+1,SUM(M373:M375),M375+800.06,M375+87.39)	None	**Not applied at all. This prevents use of generic docetaxel price.**
Mod_11 Re-estimated monitoring costs	Parameters!E163 =IF(Mod_11=0,3%,100%) Resource!C163 =IF(Mod_11=0, IF(CTscanNumber=1,1, IF(CTscanNumber=2,0.5, IF(CTscanNumber=3,0.25, IF(CTscanNumber=4,0.125, IF(CTscanNumber=5,0))))),0.25) Resource!C164 =IF(Mod_11=0, IF(ConsVisitNumber=1,1, IF(ConsVisitNumber=2,0.5, IF(ConsVisitNumber=3,0.25, IF(ConsVisitNumber=4,0.125, IF(ConsVisitNumber=5,0))))),0.25)	Parameters!E163=100% Resource!C163= IF(CTscanNumber=1,1, IF(CTscanNumber=2,0.5, IF(CTscanNumber=3,0.25, IF(CTscanNumber=4,0.125, IF(CTscanNumber=5,0))))) Resource!C164 = IF(ConsVisitNumber=1,1, IF(ConsVisitNumber=2,0.5, IF(ConsVisitNumber=3,0.25, IF(ConsVisitNumber=4,0.125, IF(ConsVisitNumber=5,0)))))	Correctly applied
Mod_12 Terminal care costs	Resource!H45 =IF(Mod_12=0,(E45/UKCPI_08) *UKCPI_11,E46) Resource!!E46 = 3906.31	Resource!H45 = 3906	Applied correctly with very minor variation (31p per patient)
Mod_13 ERG survival models	Changes to BSC worksheet AZ7, AZ10:AZ366, AW11:AW366, AX11:AX366 Changes to Pem worksheet AY7, AZ10:AZ366, AW11:AW366, AX11:AX366	None	**Not implemented at all**

7 REFERENCES

1. National Institute for Health and Care Excellence (NICE). NICE Technology Appraisal Guidance[TA309]. 2014 [April]; Available from: https://www.nice.org.uk/guidance/ta309/chapter/1-Guidance.
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